AT

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,125	03/28/2001	Etsuya Matsutani	2556USOP	7053

23115 7590 06/09/2004

TAKEDA PHARMACEUTICALS NORTH AMERICA, INC
INTELLECTUAL PROPERTY DEPARTMENT
475 HALF DAY ROAD
SUITE 500
LINCOLNSHIRE, IL 60069

EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,125	MATSUTANI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20010328*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The election with traverse filed March 3, 2004 is acknowledged and has been entered. Applicant has elected the species of invention, wherein said hormonal agent is the peptide of SEQ ID NO: 1, or a salt thereof, wherein the sixth amino acid residue is D-leucine and the ninth amino acid residue is proline-NH-C_2H_5 and said cell growth factor is EGF or a substance possessing substantially the same activity as EGF.

Claims 1-11 read on the elected invention.

2. Claims 1-11 are pending in the application and, insofar as the claims are drawn to the elected species of invention, are currently under prosecution.

Election/Restrictions

3. Applicant's traversal of the restriction and election requirement set forth in the paper filed March 3, 2004 is acknowledged. Applicant has argued the requirement is improper because the unification of species would not unduly burden the Examiner in making a search.

Applicant's remarks have been carefully considered, but Applicant's argument has not been found persuasive for the following reason:

In reply to Applicant's argument, unification of the species of invention would not unduly burden the Examiner, the burden of search is not a criterion for restriction in the instant application, since the application is a National stage entry of PCT Application No. PCT/JP99/05533. Under PCT Rule 13.1, it is proper to restrict species of invention, which do not relate to a single general inventive concept.

Accordingly, the restriction and election requirement is deemed proper and therefore made FINAL.

Sequence Rules Compliance

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for

the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

(a) Applicant has not used the proper nomenclature in designating the sequence at positions 6 and 9, since 37 CFR § 1.822 does not provide for the use of "Y" and "Z" in amino acid sequences; see MPEP § 2423. For example, at page 8 and 9, paragraph [18] reads: "As an LH-RH agonist, there may be used, for example, a peptide represented by General Formula [II]: 5-oxo-Pro-His-Trp-Ser-Tyr-Y-Leu-Arg-Pro-Z (SEQ ID NO:1)". Because the sequence listing is compliant with the requirements set forth under 37 CFR §§ 1.821-1.825, whereas the specification is not, sequences depicted in the sequence listing and sequences depicted in the specification, which are identified by the same sequence identification number, appear different, since the nomenclature used is different.

(b) In addition, although the sequence listing uses proper nomenclature, the listing of SEQ ID NO: 1 fails to correctly identify each of the five possible residues that can occur at position 6 of the sequence and each of the two possible residues that can occur at position 9 of the sequence. The present listing of SEQ ID NO: 1 indicates only that the residue at position 6 is D-leucine and the residue at position 9 is N-ethyl-L-prolinamde, whereas the specification indicates the residue at position 6 is one of five possible residues and the residue at position 9 is one of two possible residues.

As noted in the attached Notice to Comply, appropriate actions correcting these deficiencies are required.

Specification

5. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of improperly demarcated trademarks include Adriamycin™ (page 18, paragraph [60]) and Taxol™ (page 18, paragraph [60]).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 9 and 10 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3 and 6-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3 and 6-8 are drawn to a composition comprising "a hormonal agent". Claim 2 is drawn to the composition of claim 1 wherein the hormonal agent is "a LH-RH derivative". Claim 3 is drawn to the composition of claim 2 wherein the LH-RH derivative is "an LH-RH agonist". Claim 6 is drawn to the composition of claim 1 containing "an agent that inhibits the action of a cell growth factor or a receptor thereof". Claim 7 is drawn to the composition of claim 6 wherein the cell growth factor is EGF "or a substance possessing substantially the same activity as [EGF]". Claim 9 is drawn to a method for using "a hormonal agent". Claim 10 is drawn to a method for producing "a pharmaceutical". Claim 11 is drawn to a method comprising administering "a hormonal agent".

The specification adequately describes a peptide comprising SEQ ID NO: 1, wherein the sixth amino acid residue is D-leucine and the ninth amino acid residue is proline-NH-C_2H_5. In addition, the specification adequately describes other similar peptides, but the genus of "hormonal agents" to which the claims are directed, whether the agents be limited to an LH-RH derivative or even an LH-RH agonist, is composed of members so widely variant in structure and function that the description of SEQ ID NO: 1 cannot be reasonably considered descriptive of the whole of the genus, nor can the description be considered representative of the whole of the genus.

Similarly, PD153035 cannot be reasonably be regarded as representative of the genus of agents that inhibit the action of a cell growth factor or receptor thereof; nor of the genus of agents that inhibit EGF or it receptor, or another substance that possesses substantially the same activity as EGF, because, here again, the members of the genus vary markedly in structure and function. In both instances, the specification fails to disclose a particularly identifying feature that is common to at least a substantial number of members of the genera, which might serve to enable the skilled artisan to immediately recognize, envision, or distinguish at least a substantial number of their members.

Furthermore, the members of the genus of substances possessing substantially the same activity as EGF, or any other cell growth factor or receptor thereof, cannot be regarded as adequately described, since, here again, the members of the genus are so very different.

Accordingly, the written description of the claimed invention set forth in Applicant's specification is not adequate to reasonably convey to the skilled artisan that Applicant had

possession of the claimed invention at the time the application was filed, because even given benefit of Applicant's disclosure, the skilled artisan could not instantly recognize, envision, or distinguish at least a substantial number of the members of the genus of "hormonal agents" to which the claims are directed. The skilled artisan could not instantly recognize, envision, or distinguish at least a substantial number of the members of the genus of "LH-RH derivatives" to which the claims are directed. The skilled artisan could not instantly recognize, envision, or distinguish at least a substantial number of the members of the genus of "LH-RH agonists to which the claims are directed; nor could the skilled artisan instantly recognize, envision, or distinguish at least a substantial number of the members of the genus of agents that inhibit the action of a cell growth factor or its receptor. Finally, the skilled artisan could not instantly recognize, envision, or distinguish substantial number of the members of substances possessing substantially the same activity as EGF to which the claims are directed.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing

distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

Furthermore, in deciding *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the Court held that a generic statement that defines a genus of nucleic acids, or more aptly in this instance, a genus of agents *by only their functional activity* does not provide an adequate written description of the genus. Furthermore, the Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

10. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a composition for repressing proliferation of

hormone-dependent prostate cancer, said composition comprising the peptide of SEQ ID NO: 1, or a salt thereof, wherein the sixth amino acid residue is D-leucine and the ninth amino acid residue is proline-NH-C_2H_5, and the tyrosine kinase inhibitor PD153035, does not reasonably provide enablement for making and using a composition for retarding the transformation of a hormone-dependent cancer to a non-hormone dependent cancer and does not reasonably provide enablement for making and using a composition for preventing prostatic cancer, ovarian cancer, cervical cancer, or breast cancer, wherein said composition comprises any hormonal agent and any agent that inhibits the action of a cell growth factor or receptor thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-8 are drawn to a composition comprising a genus of hormonal agents, which can be used to retard the transformation of a hormone-dependent cancer to a hormone-dependent cancer, or which can be used to treat or prevent prostate cancer, ovarian cancer, cervical cancer, or breast cancer. Claims 6 and 7 are drawn to the composition of claim 1 further comprising an agent that inhibits the action of a cell growth factor or a receptor thereof, wherein said growth factor is EGF or a substance that possesses substantially the same activity as EGF. Claims 9 and 11 are drawn to a method for retarding the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer comprising using or administering to a mammal a hormonal agent or a composition comprising a hormonal agent, respectively. Claim 10 is drawn to a method for producing a pharmaceutical using a hormonal agent.

The teachings set forth in the specification are not reasonably commensurate in scope with the claims. Moreover, the amount of guidance, direction, and exemplification set forth therein would not be sufficient to enable the skilled artisan to make and use the claimed invention without having to first perform an undue amount of additional experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the

quantity of experimentation which would be required in order to make and use the invention as claimed.

Regarding making the claimed invention, the specification teaches the LH-RH antagonist, cyproterone, but apart from the peptides of claim 4, the specification fails to teach one to make other hormonal agents, including LH-RH derivatives and LH-RH agonists. Furthermore, although the specification teaches the tyrosine kinase inhibitor, PD153035, the specification fails to one to make other agents that are capable of inhibiting the action of a cell growth factor or its receptor, including EGF and its receptor. The specification fails to teach other substances that possess substantially the same activity as EGF, so it follows the specification also fails to teach one to make agents that are capable of inhibiting the action of these other substances. Accordingly, the teachings of the specification are not reasonably commensurate in scope with the claims and the skilled artisan could not make the claimed invention without having to perform an undue amount of additional experimentation, since one cannot instantly envision the hormonal agents or the agents that inhibit the activity of a growth factor or its receptor, which can be used to retard the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer or, for that matter, to repress proliferation of hormone-dependent prostate cancer.

Regarding the use of the claimed invention, the prevention of cancer is intractable. The specification fails to show that the claimed invention can be used to prevent cancer. Therefore, the skilled artisan would not accept the assertion that the claimed invention can be used to prevent prostate cancer, ovarian cancer, cervical cancer, or breast cancer. Nevertheless, the specification fails to teach how one should practice the claimed invention to prevent cancer, since the specification fails to provide any guidance or direction as to how subjects should be selected for treatment with the claimed invention.

In addition, while the specification shows that agents, such as PD153035 and cyproterone, can be used to inhibit the growth of LNCaP prostate cancer cells, the specification fails to demonstrate that the claimed invention can retard the transformation of hormone-dependent cancer to hormone-independent prostate cancer. As the specification discloses at page 10, prostate cancer typically becomes unresponsive to hormone therapy over the course of treatment. Even though the growth of hormone-responsive prostate cancer can be suppressed,

the cancer eventually becomes unresponsive. Susuki et al. (*Endocr. Relat. Cancer.* **10**: 209-216, 2003), for example, teaches almost all prostate cancer patients initially respond to hormonal therapy, but the majority gradually develop resistance; see, e.g., the abstract. Applicant's have provided no factual evidence that the skilled artisan would accept as a showing that Applicant's invention has overcome the problem that prostrate cancer eventually becomes hormone insensitive. Moreover, administering many hormonal agents to a mammal will not retard the transformation of hormone-dependent cancer to a non-hormone-dependent cancer, since there are many hormones; growth hormone, for example, is not expected to be capable of inhibiting the growth of hormone- dependent cancer, much less retard its transformation to a hormone insensitive state.

Furthermore, while the specification suggests a peptide comprising SEQ ID NO: 1, wherein the sixth amino acid residue is D-leucine and the ninth amino acid residue is proline-NH-C_2H_5, might be used to inhibit the growth of prostate cancer, even given benefit of Applicant's disclosure, the skilled artisan could not make or use at least a substantial number of the members of the "hormonal agents" to which the claims are directed, since the specification fails to teach how other agents can be made, which can be used in practicing the claimed methods. Similarly, the skilled artisan could not make or use at least a substantial number of the members of the genus of agents that inhibit the action of a cell growth factor or receptor thereof, including those that inhibit EGF or it receptor, or any other substance that possesses substantially the same activity as EGF, because, here again, the specification fails to teach how these agents can be made.

The specification shows that PD153035, a tyrosine kinase inhibitor, and cyproterone, an androgen antagonist, can be used to inhibit the growth of androgen-dependent prostate cancer cells. However, it is well known that the art of drug discovery for is highly unpredictable. For example, Gura (*Science* **278**: 1041-1042, 1997) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Moreover, because of the lack of predictability in the art, Gura discloses that often researchers

merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

Accordingly, the amount of guidance, direction, and exemplification set forth therein would not be sufficient to enable the skilled artisan to make and use the claimed invention in a manner that is reasonably commensurate in scope with the claims without having to first perform an undue amount of additional experimentation. Therefore, the specification fails to provide a sufficiently enabling disclosure, as required under 37 USC § 112, first paragraph.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 10 provide for the use of a hormonal agent, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process Applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-3 and 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Schally et al. (*Proc. Natl. Acad. Sci. USA* **84**: 7275-7279, 1987).

Claims 1-3 and 6-8 are drawn to a composition comprising a genus of hormonal agents, which can be used to retard the transformation of a hormone-dependent cancer to a hormone-dependent cancer, or which can be used to treat or prevent prostate cancer, ovarian cancer, cervical cancer, or breast cancer. Claims 6 and 7 are drawn to the composition of claim 1 further comprising an agent that inhibits the action of a cell growth factor or a receptor thereof, wherein said growth factor is EGF or a substance that possesses substantially the same activity as EGF. Claims 9 and 11 are drawn to a method for retarding the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer comprising using or administering to a mammal a hormonal agent or a composition comprising a hormonal agent, respectively. Claim 10 is drawn to a method for producing a pharmaceutical using a hormonal agent.

At page 10 (paragraph [24]), the specification discloses:

> "To retard the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer (transformation is retarded)" means that in applying hormone therapy to a hormone-dependent cancer described above, the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer is retarded by suppressing or retarding the proliferation of a cancer that has become unresponsive to hormone therapy as a result of a long-term administration of a hormonal agent (non-hormone-dependent cancer).

Accordingly, the claimed compositions and methods for retarding the transformation of a hormone-dependent cancer to a hormone-dependent cancer are interpreted as claims to composition and methods for suppressing or retarding proliferation of a cancer, such that its progression to a non-hormone-dependent state is suppressed or retarded.

Schally et al. teaches the production and use of a composition of a combination of an LH-RH agonist and an inhibitor of EGF activity; see entire document, particularly the abstract; and the paragraph bridging pages 7275 and 7276. Schally et al. teaches the combination can be used to treat prostate cancer; see, e.g., the abstract. Schally et al. teaches the treatment inhibits the growth of the prostate cancer cells; see, e.g., the abstract. Accordingly, Schally et al. teaches a composition and methods for suppressing or retarding proliferation of a cancer, such that its progression to a non-hormone-dependent state is suppressed or retarded, wherein said composition comprises an LH-RH agonist and an inhibitor of EGF activity. Schally et al. teaches the inhibitor of EGF activity, namely the somatostatin analogs enhance the inhibitory effects of the LH-RH agonist; see, e.g., the abstract.

15. Claims 1-3 and 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Pinski et al. (*Cancer* **72**: 3263-3270, 1993).

An analysis of the claims is set forth above.

Pinski et al. teaches a composition of a combination of an LH-RH agonist and an inhibitor of EGF activity; see entire document, particularly the abstract; and page 3264, column 1. Pinski et al. teaches the combination can be used to treat prostate cancer; see, e.g., the abstract. Pinski et al. teaches the treatment inhibits the growth of the prostate cancer cells; see, e.g., the abstract. Accordingly, Pinski et al. teaches a composition and methods for suppressing or retarding proliferation of a cancer, such that its progression to a non-hormone-dependent state is suppressed or retarded, wherein said composition comprises an LH-RH agonist and an inhibitor of EGF activity. Pinski et al. teaches combination had the greatest effect on tumor growth; see, e.g., the abstract.

16. Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/32423 A1 (of record), as evidenced by Schally et al. (*Proc. Natl. Acad. Sci. USA* **84**: 7275-7279, 1987) and/or Pinski et al. (*Cancer* **72**: 3263-3270, 1993).

An analysis of the claims is set forth above.

As evidenced by Schally et al., somatostatin derivatives, such as those disclosed by WO 98/32423 A1 at, e.g., page 10, line 35, through page 11, line 11, are agents that inhibit the activity of EGF or its receptor.

As evidenced by Pinski et al., bombesin peptide, such as that disclosed by WO 98/32423 A1 at, e.g., page 11, line 25, is an agents that inhibits the activity of EGF or its receptor.

WO 98/32423 A1 teaches a the production and use of a composition of the peptide of SEQ ID NO: 1, or a salt thereof (particularly, acetate), wherein the sixth amino acid residue is D-leucine and the ninth amino acid residue is proline-NH-C_2H_5; see entire document, particularly page 13, lines 27-36. WO 98/32423 A1 teaches the peptide is an LH-RH agonist; and moreover, the prior art teaches a composition of the LH-RH agonist and either a somatostatin derivative or bombesin, or both, can be used to treat diseases dependent on LH-RH or hormones induced thereby, including prostate cancer, cervical cancer, ovarian cancer or breast cancer; see, e.g., the

abstract; page 8, lines 13-16; page 10, line 32, through page 12, line 9; page 13, lines 27-36; page 37, lines 26, through page 38, page 17; and claim 56.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1-3 and 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,211,215 B1.

US Patent No. 6,211,215 B1 ('215) teaches a method for inhibiting tumor growth of hormone dependent prostate cancer comprising administering an inhibitor of tyrosine kinase activity, including the tyrosine kinase activity of the EGF receptor; see entire document, particularly, e.g., the abstract; column lines 42-57; column 1, line 65, through column 2, line 52. For example, at columns 29 and 30, '215 teaches inhibiting prostate cancer with such a compound. In addition, '215 teaches the present invention may be used more effectively in combination with conventional treatments, such as hormone therapy; see, e.g., column 30, lines 13-24. At column 22, lines 5-14, '215 teaches as an example of such hormone therapy that can be used in combination with the claimed invention, LH-RH agonists, e.g., leuprorelin and goserelin, are suitable.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a composition comprising an inhibitor of tyrosine kinase activity, as taught by '215, and an LH-RH agonist, e.g., leuprorelin and goserelin, because '215 suggests the combination can be used more effectively treat prostate cancer. One of ordinary skill in the art would have been motivated to do so to treat prostate cancer.

19. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schally et al. (*Proc. Natl. Acad. Sci. USA* **84**: 7275-7279, 1987), or Pinski et al. (*Cancer* **72**: 3263-3270, 1993), or US Patent No. 6,211,215 B1, in view of WO 98/32423 A1.

Schally et al., Pinski et al., and US Patent No. 6,211,215 B1 ('215) teach that which is set forth above.

However, none of Schally et al., Pinski et al., and '215 teach or suggest an LH-RH agonist, which is the peptide of SEQ ID NO: 1, or a salt (acetate) thereof, wherein the sixth amino acid residue is D-leucine and the ninth amino acid residue is proline-NH-C_2H_5.

WO 98/32423 A1 teaches that which is set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a composition comprising an inhibitor of tyrosine kinase activity, as taught by '215, and the peptide of SEQ ID NO: 1, or a salt thereof, and particularly the acetate thereof, wherein the sixth amino acid residue is D-leucine and the ninth amino acid residue is proline-NH-C_2H_5, according to WO 98/32423 A1, because each of none of Schally et al., Pinski et al., and '215 suggest the combination of the inhibitor of tyrosine kinase activity and an LH-RH agonist can be used more effectively treat prostate cancer. One of ordinary skill in the art would have been motivated to do so to treat prostate cancer.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-30 of U.S. Patent No. 6,716,863 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and issued claims are drawn to nearly the same compositions comprising an LH-RH agonist and an agent that inhibits the action of EGF and its receptor, or nearly the same methods for producing the composition or using the composition to treat cancer. For clarity, claim 30 of the patent recites the LH-RH antagonist is "leuprorelin or a salt thereof". An acetate salt of leuprorelin is "leuprolide", which is a generic drug sold under a variety of different tradenames, e.g., **ELIGARD®** leuprolide acetate is a peptide having the structure recited in claim 5 of the instant application.

22. Claims 1-11 are directed to an invention not patentably distinct from claims 5-30 of commonly assigned U.S. Patent No. 6,716,863 B2. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reason set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent No. 6,716,863 B2, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

23. Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-39 of copending Application No. 10/620,706. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and issued claims are drawn to nearly the same compositions comprising an LH-RH agonist and an agent that inhibits the action of EGF and its receptor, or nearly the same methods for producing the composition or using the composition to treat cancer. For clarity, claim 18 of the copending application recites the LH-RH antagonist is "leuprorelin or a salt thereof". An acetate salt of leuprorelin is "leuprolide", which is a generic drug sold under a variety of different tradenames, e.g., **ELIGARD®** leuprolide acetate is a peptide having the structure recited in claim 5 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 1-11 are directed to an invention not patentably distinct from claims 9-39 of commonly assigned copending Application No. 10/620,706. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reason set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/620,706, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

Conclusion

25. No claims are allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
June 1, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No.	Applicant(s)	
	09/806,125	MATSUTANI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: If necessary to correct the deficiency, Applicant is required to submit substitute copies of the sequence listing together with a statement, as indicated below.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY